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Therapeutic Products Programme

POINTS-TO-CONSIDER

Points to Consider when Reviewing Therapeutic regimens for Eradication of *Helicobacter pylori* in GI diseases

DRAFT

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Therapeutic Products Programme
POINTS-TO-CONSIDER

Points to Consider when Reviewing Therapeutic regimens for Eradication of *Helicobacter pylori* in GI diseases

1. INTRODUCTION

1.1 PURPOSE

The purpose of this document is to suggest points for consideration when designing clinical trials dealing with eradication of *H. pylori* in GI diseases and to outline elements to be reviewed. The document is not intended to be exhaustive but to ensure that the studies and their subsequent review are carried out in a consistent manner.

Basic clinical trial design must comply with the current ICH Good Clinical Practice: Consolidated Guidelines (GCP). Specific considerations in relation to methodology, study end-points, definition of outcome, definition of infection and selection of subjects are presented.

Alternate approaches to the principles and practices described in this document may be acceptable provided they are supported by adequate scientific justification. Submission sponsors are encouraged to discuss, in advance, alternate approaches with the to avoid the withdrawal or rejection of a submission.

1.2 BACKGROUND

H. pylori was first found in gastric biopsy specimens in association with gastritis in 1980. While the association between *H. pylori* and peptic ulcer disease is now recognized, the involvement of *H pylori* in other GI diseases is still under investigation: e.g., non-ulcer dyspepsia, history of gastric /duodenal ulcers, NSAID-induced ulcers with H. pylori positive status, gastric cancer (gastric adenocarcinoma, mucosa-associated lymphoid tissue, and non-Hodgkin's lymphoma).

Points-to-Consider (PTCs) are developed to provide advice on selected issues relating to the development and evaluation of therapeutic products. PTCs typically serve as a means of documenting acceptable approaches to regulatory requirements in areas where rapid and ongoing change preclude the development of formal guidance documents. PTCs are intended to be revised in accordance with scientific advances.

This and other Guidance Documents are available on the Therapeutic Products Programme (TPP) Website (**http://www.hc-sc.gc.ca/hpb-dgps/therapeut**). Guidelines listed on the Directorate's *Guidelines Order Form* are available in printed form only, through the Canadian Government Publishing Centre (CGPC). The *Order Form* is available on the TP Website under "Forms" or from the CGPC (Tel: 819-956-4800; Fax: 819-994-1498; Internet: http://publications.pwgsc.gc.ca).

It has been generally accepted that eradication of *H. pylori*, assessed at least 4 weeks after completion of therapy, may be used as a surrogate for investigating the reduction of peptic ulcer recurrence. The healing of duodenal ulcers is determined at least 4 weeks following the end of treatment; a follow-up to demonstrate decrease in recurrence of peptic ulcers is not required. There is insufficient scientific/medical information in the literature to accept eradication of *H. pylori* as surrogate for prevention of recurrence in other GI diseases; therefore, at the present time, follow-up studies should be carried out.

Treatment of *H. pylori* infection may require use of dual, triple or quadruple therapies. Triple therapies refer to a combination of three medications including, generally, antisecretory drugs (PPI or H2 antagonist) plus antimicrobials. These therapies have shown eradication rates of 80% or larger after a relatively short treatment period. However, there is still room for improvement. Not all possible triple drug combinations have been subjected to clinical trials; nor do we know either the place of possible quadruple therapies. Finally, more and better drug regimens may be developed in the future to eradicate *H. pylori*.

1.3 SCOPE

This guide addresses specifically issues on clinical trial design for the demonstration of eradication of *H. pylori* in patients with duodenal ulcers. Other elements included address aspects of such submissions relevant to regulatory requirements and to studies carried out for other *H. pylori*-associated GI diseases.

2. ACTIVE DUODENAL ULCER DISEASE - MINIMUM TRIAL REQUIREMENTS

2.1 Clinical Trial Design

Study Design: Pivotal study(ies) should be multi-centre, double blind, concurrently controlled and randomized, and if necessary stratified according to ulcer size. The choice of the most appropriate control for any new regimen is difficult to define a priori. An antisecretory drug may be used alone or an already approved combination therapy may be considered. We discourage the use of regimens known to potentially result in the emergence of resistant strains. The study should be designed to demonstrate the need for the particular combination under investigation. Consultation with the regulatory agency is encouraged.

Study Objective: The primary objective of the study should be the eradication of *H pylori*, assessed at least 4 weeks after the end of treatment. The secondary objectives are

the healing of duodenal ulcer at least 4 weeks after the end of treatment and the disappearance of symptoms.

Inclusion Criteria: Patients to be included in the study should have active duodenal ulcers and be *H. Pylori* positive. If patients with a history of duodenal ulcers are included, the trial analysis should stratify patients into active duodenal ulcer and history of duodenal ulcer.

Exclusion Criteria: In addition to the usual exclusion criteria in these studies, the following should also be considered:

- Patients with previous exposure to drugs capable of interfering with their *H. pylori* status (antibiotics, H2 antagonists, bismuth, PPI etc.). Such patients could be included, however, if an appropriate washout period is allowed to elapse (minimum 2 weeks; four weeks are preferred. Deviations should be discussed and justified).
- Allergy to penicillins or macrolides (or to any drug of the multiple therapy).
- Previous gastric surgery.
- Patients previously treated with anti-*H. pylori* therapy, unless at least 4 weeks from the end of the previous eradication therapy are allowed to elapse.

Definition of Ulcer: Ulcers should be confirmed by endoscopy. Ulcers are defined as a lesion in the gastroduodenal mucosa that penetrates the muscularis mucosae and of ≥ 5 mm in diameter. Because of the difficulty in assessing the depth of the ulcer by endoscopy (the difficulty increases with smaller ulcers), we advise that patients are stratified as follows: > 3 mm to <5 mm and ≥ 5 mm. Clinical justification should be provided when deviations are reported.

Definition of Healing: a complete re-epithelialisation of the ulcer, with or without erythema, with re-establishment of continuity of the mucosa.

Definition of Ulcer relapse: a reappearance of a lesion as defined above.

***H. pylori* status:** *H. pylori* should be diagnosed with at least two distinct testing methodologies (Hopkins et al., 1996; Megraud 1997). Until now, no single technique has been considered to be ideal for the detection of *H. pylori*. The combination of at least two tests is encouraged: in spite of high specificity, a sensitivity of 90% has been not considered high enough to allow one test alone to be used as diagnostic test after treatment, while a combination of two tests gave a sensitivity of 99% (Megraud 1997). In addition, the sensitivity and specificity of a test do not take into consideration the inherent variability in determining the value of many laboratory tests nor the intra- and inter-rater reliability.

Endoscopically based tests are desirable as experience is abundant (culture, histology with specific staining for H pylori, urease test [CLOtest]). Culture is considered the "gold standard" test and if positive, this test alone suffice. The non-invasive urea breath tests (UBT) is acceptable, when the appropriate validation of the test at each corresponding testing site is provided. If UBT is acceptable, the second test should be either culture or histology (using the Genta or Giemsa or Warthin-Starry stain). For now, it is desirable that the selected tests (at least two) base their results on different assay methodologies. The CLOtest and UBT both measure urease activity in the stomach; the CLOtest is a local test while the UBT is a global test. The specificity of the urease test (CLOtest and UBT) when other urease-producing organisms are colonizing the gastric mucosa needs further clarification/considerations.
Concordance between tests (at the pre-entry and post treatment phase) should be presented in the submission, analysed and commented on.

Although the CLOtest was the first rapid urease test to be developed, other commercially available tests may be used with appropriate validation. The CLOtest has been recommended not to be used as the post-treatment test because of relatively low sensitivity, especially in patients treated with urease inhibitors, such as PPIs. In fact, it does not provide useful information and jeopardizes blinded testing with regard to Hp status.

Serology based tests are considered acceptable for epidemiological studies or screening purposes prior to eradication therapy but not for evaluation of infection status in clinical trials. *H. pylori* -saliva based tests have been developed but they are not currently accepted.

Definition of H pylori Status:

Pre-treatment: **if two tests** give positive results, the status is classified as "infected" and therefore evaluable, otherwise " negative" or unevaluable. Presently, only results from the culture test are given more weight than results from other tests. If the culture test is positive and the other test is unevaluable or negative, the status is classified as "infected".

Post-treatment: **if two tests** give negative results and no test gives a positive result, the status is classified as "eradicated" in both the "Modified Intent to Treat" (MITT) and "Per Protocol Analysis" (PP) analysis. If one positive test is found either alone or with other tests with negative or missing results, the status is classified as "persistent". If one test is negative and the other is missing or unevaluable, the status is classified as "unevaluable" and excluded from the PP analysis but included as "failure" in the MITT analysis. The diagnostic status based on the two (or more) tests should be clearly described.

Endoscopic examinations: all patients at pre and post treatment should be endoscoped to obtain biopsies and to document the presence, size and location of duodenal ulcer(s) and other lesions.

Biopsies: Appropriate number of biopsies from antrum and corpus should be taken for assessment of infected status and for microbial sensitivity testing (if the antibiotic regimen contains an antibiotic to which H pylori may be resistant). The number and site of biopsies should be indicated in the submission. Currently at least 2 biopsies from both antrum and corpus may be adequate for the DU studies.

Withdrawal of patient: Reasons for withdrawal of patients from the study should be clearly indicated. Patients withdrawn due to adverse reactions related to the study medication or to progression of disease should **be included as "failures" in the PP analysis**.

Protocol Violation should be specified. A violation is considered major when patients:

- received less than 80% of study medication.
- received treatment for less than 80% of the treatment time sought.

Figures between 70-80% may be acceptable after thorough review of the file.

Populations: Intent to Treat population (ITT): all patients randomized to one of the treatment groups regardless of the Hpylori status, with documented duodenal ulcer.

Modified ITT population (MITT): A subset of the ITT population: those patients who are *H. pylori* positive at prestudy and have duodenal ulcer.

Evaluable or Per Protocol population (PP): a subset of MITT who adhere to the protocol throughout the study.

On Data Analysis:

Primary efficacy analyses :

- *H. pylori* eradication rate is the % of patients with a negative *H. pylori* status at ≥ 4 weeks following the end of treatment among those patients in the MITT or PP population. For the MITT analysis, failure is defined as those patients who have a positive *H. pylori* status (infected) at ≥ 4week following end of treatment, those who were prematurely withdrawn, those who dropout from the study, and those who had a follow-up visit < 4 weeks following the end of treatment. These patients are included in the MITT analysis as failures.

For the PP analysis, failure is defined as those patients who have a positive H pylori status (infected) at ≥ 4week following end of treatment, those who drop out due to the study medication or progression of the disease, and those who had a follow-up visit <4 weeks following the end of treatment with a positive H pylori status. These patients are included in the PP analysis as failures.

Secondary efficacy analyses:

- Ulcer healing rate is the % of patients with healed ulcers at or after 4 weeks following the end of treatment among the MITT and PP population, based on endoscopic evaluation .

- GI symptoms: the disappearance of symptoms or significant improvement of symptoms after treatment assessed using a validated symptom score questionnaire should be documented.

Special considerations should be given to associated mucosal pathological findings in the GI-Hp diseases. The status of gastritis, mucosal atrophy and/or intestinal metaplasia changes should be reported. [Note: it is preferred that the definition of gastric atrophy be standardized (see Genta 1998)]. At the present time, if it is possible, the manifestation of reflux esophagitis should be documented.

Sensitivity to the antibiotic coprescribed: This should be determined in patients who fail therapy (remained *H. pylori* positive). For microbiological considerations the FDA Guidelines should be consulted (Feb 1997, pages 81-85).

2.2 Clinical Trials with other objectives:

- **History of peptic ulcers:** patients with Inactive (healed) Peptic Ulcer Disease represent a heterogenous population in term of risk of ulcer recurrence. Patients whose ulcers have been recently healed are at higher risk of ulcer recurrence as compared to those who have their ulcers healed for a longer period of time. It is, then, recommended that patients with history of peptic ulcer (gastric or duodenal) disease be stratified according to the length of time the ulcers have been inactive. At the present time, there is limited evidence that the eradication of Hp in patients with history of peptic ulcers is associated with decrease in ulcer recurrence. Therefore, it is important that the study design includes endoscopy at pre- and post- treatment to assess both *H pylori* and ulcer status. The follow-up period should be at least 6 month following completion of *Hp* eradication therapy. When using an accepted therapeutic regimen for eradication of H pylori, placebo (or H2-antagonist or PPI) may be used as the control group to which the study therapy can be compared to. In patients who are on maintenance antisecretory therapy because of high risk of serious GI events (eg., elderly patients using NSAID and with a history of GI events, such as ulcer perforation or bleeding) discontinuation of the

maintenance therapy is not ethical, for safety reasons. Therefore, their inclusion is considered problematic unless the trial is not placebo controlled.

- **Non-ulcer dyspepsia or functional dyspepsia** refers to a chronic or recurrent condition defined as pain or discomfort centred in the upper abdomen. Symptoms are usually present for at least 3 months and oesophageal-gastro-duodenal endoscopy has excluded peptic ulceration, reflux oesophagitis and malignancy. This group includes patients with histological gastritis associated with *H. pylori* infection in the absence of ulcers or erosions. The presence or absence of gallbladder disease should be documented by ultrasound.

Patients with Gastroesophageal Reflux Disease (GERD) are not considered to have non ulcer dyspepsia (even if they do not have endoscopic oesophagitis). When symptoms such as heartburn and reflux are the predominant symptoms in dyspeptic patients they are considered as having GERD.

The study design for nonulcer dyspepsia should be double blind, placebo controlled and randomized. Symptom relief is the principal end point of the study. *H. pylori* infection at pre- and post-treatment should be assessed by two methods as discussed before. However, when an approved treatment (eradication rate >80% MITT) is used, post-treatment evaluation of eradication may be performed with one test only, in particular the UBT which is carried out twice with a two month interval. Once eradication has been confirmed, only one UBT could be acceptable in the follow-up phase. The follow-up period should be long enough (6-12 months) to ensure lack of symptoms recurrence.

Methods or instruments for measuring symptoms should be validated (see Talley 1994 and Veldhuyzen van Zanten et al.,1993).

2.3 Other issues

Bioequivalence : When various drugs are to be combined for treatment purposes (co-therapy), it is desirable that each of the drugs be an approved Canadian formulation. When the studies are conducted in other countries, are multinational and the drugs used are not the Canadian formulation then, the sponsor should provide assurance that all non-Canadian drug products are as safe and effective as the Canadian reference product (s). Conducting comparative bioavailability studies is one way to provide this assurance. However, the TDP is prepared to review indirect demonstration of equivalence based on data from the public domain. The use of published clinical trials to justify the exchange of formulations/products is acceptable if the sponsor shows that the outcome (i.e., the response rates as recorded) from the different studies are within the same range. The

published clinical trials should qualify as Level 1 evidence and have the same study design; only the formulation is different.

When direct bioequivalence studies are considered, input from the Division of Pharmaceutical Equivalence (DPE) should be sought. Manufacturers are encouraged to consult the TPD before deciding on the type of evidence they intent to provide for demonstrating the bioequivalence of the drugs.

Doses: It is desirable that the doses proposed for co-therapies should not exceed the dose recommended in the Product Monograph of each individual drug. Higher doses introduce new complexities concerning the safety of the product (s). This is particularly important with co-therapies when drugs are metabolized by the same enzyme system. Manufacturers should address these issues when developing regimens to eradicate *H. pylori*.

A particular dilemma is posed when marketed strengths differ from those used in pivotal trials (e.g. metronidazole 400 mg vs 500 mg tablets). The validity of these trials is doubtful unless the manufacturer shows directly or indirectly (published data that qualify as Level 1 evidence and have the same study design) that such exchange has no impact on the safety (and/or efficacy) of the regimen proposed.

Length of Treatment: The proposed treatment period should be fully supported by the pivotal clinical trials.

There is a tendency to shorten the eradication treatment period from 2 weeks to 1 week and recently to 3 days or even one day therapy. *A priori,* there is no reason why a clinical trial in which a short term therapy is sought, should not be carried out. However, for short term therapies (<1 week) , there is the risk of infection recrudescence and/or the development of secondary antimicrobial resistance. Patients enrolled in short term trials should be followed up (eradication tests and endoscopy) for at least 12 weeks following discontinuation of drugs.

There are no clear data on whether patients who fail one regimen may be less responsive to another regimen: this issue required further elucidation.

Drug Interaction Studies: Bioavailability studies should be conducted for each of the medicines of the multiple therapy alone and in the proposed dosage combination.

In general, Level 1 evidence are results from randomized, double-blinded and controlled clinical trials. For Hpylori studies the design should also follow the minimal recommendation proposed in this guide (such as: at least two tests to assess H pylori status, a well defined patient population, proper quantitative clinical endpoints).

Study drug bioavailability should be conducted in the presence and absence of the coprescribed medicines (antibacterials). For dual therapies, the antisecretory drug (ASD) with and without an antibacterial should be compared. Ideally, for triple therapy (ASD plus 2 antibacterials): ASD bioavailability should be compared to ASD bioavailability in the presence of the two antibacterials.

Similarly, for each antibacterial, the corresponding bioavailability should be compared with that found in the presence of the other two medicines (antisecretory plus antibacterial). Studies should use the doses proposed in the therapeutic trials.

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September 28, 1998 /
Le 28 septembre 1998

98-026950

To: Associations

Subject: Draft "Points to Consider when Reviewing Therapeutic Regimens for Eradication of *Helicobacter pylori* in GI disease"

The purpose of this letter is to seek your comments on the enclosed draft Points-to-Consider (PTCs) when designing clinical trials dealing with the eradication of Helicobacter pylori in gastro-intestinal (GI) diseases. In doing this, it also outlines elements in the submission to be reviewed by the Therapeutic Products Programme (TPP).

Aux : Associations

Objet : Ébauche « Facteurs à considérer au moment d'examiner des régimes thérapeutiques visant à éradiquer *Helicobacter pylori* dans les maladies gastro-intestinales »

Je vous écris pour solliciter vos commentaires sur l'ébauche ci-jointe du document Facteurs à considérer au moment de planifier des essais cliniques visant aux régimes thérapeutiques qui ont comme but d'éradiquer Helicobacter pylori dans les maladies gastro-intestinales. Ce document décrit également les éléments qui doivent faire partie des présentations soumises à l'examen de la

Division.

These PTCs have been developed to ensure that the preparation of drug submissions and the review of these submissions are carried out in a consistent manner. These PTCs complement the Therapeutic Products Programme Guidelines for Preparation of Investigat-ional New Drug Submissions and Preparation of Human New Drug Submissions.

L'élaboration de ces facteurs à considérer (FAC) vise à garantir une certaine homogénéité de des présentations de drogues et de la manière dont elles sont examinées. Ces FAC viennent compléter les lignes directrices de la Direction des produits thérapeutiques relatives à la préparation d'une présentation de drogues nouvelles de recherche et d'une présentation de drogues nouvelles à usage humain.

The following documents have been consulted:

Nous avons consulté les documents suivants :

- FDA: *Helicobacter pylori* -Associated Peptic Ulcer Disease- Indication # 25 (Draft- March 15, 1995).
- Hopkins et al., Relationship between *Helicobacter pylori* eradication and reduced duodenal and gastric ulcer recurrence: A review. Gastroenterol 1996;110:1244.
- NIH Consensus Development Panel on *Helicobacter pylori* in Peptic ulcer Disease. Jama 1994;272:65.
- Hunt et al., Canadian *Helicobacter pylori* Consensus Conference. Can J Gastroenterol 1998;12:31.
- Working Party of the European *Helicobacter pylori* Study Group. Guidelines for clinical trials in *Helicobacter pylori* infection. Gut 1997;41:S2.
- Veldhuyzen van Zanten. The role of *Helicobacter pylori* infection in non-ulcer dyspepsia. Aliment Pharmacol Ther 1997;11 (Suppl. 1),:63.

- FDA: Evaluating clinical studies of antimicrobials...(Draft- Feb 17, 1997).
- Megraud F. Diagnosis and candidates for treatment of *Helicobacter pylori* infection.Gastroenterol 1997;113:S93.

These Points-to-Consider are intended to be a guide. As new and relevant information become available, these will be incorporated, as appropriate.

Ces facteurs à considérer se veulent un guide. Au fur et à mesure que de nouveaux renseignements pertinents seront mis au jour, ils seront intégrés à ce document.

Please provide your comments by November 30, 1998 to:

Nous vous invitons à nous faire parvenir vos commentaires d'ici le 30 novembre 1998 à :

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Enclosure

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cc: PMC / CGP